REMARKS

By the present amendment, Applicants have canceled Claims 1-15 and 274 without prejudice or disclaimer of the subject matter described therein. Claim 275 was presented with Applicants' Preliminary Amendment dated August 6, 2004, which is a substantial copy of pending Claim 6 of the Short '449 patent. By the present Amendment, Claim 275 is amended to insert "b)" in front of the first word ("reassembling") of the second step in the claim. The '449 patent issued on August 12, 2003, and as such, Applicants have complied with 35 U.S.C. §135(b)(1). Exemplary support for Claim 275 can be found throughout the specification and claims as originally filed, at least as shown in Appendix A, attached.

No new matter has been added by the present amendment. Applicant reserves the right to file a continuation or divisional application directed to any or all subject matter that may have been canceled in this application.

Request for Interference

Applicants present this Amendment in conjunction with a Request by Applicants for Interference Pursuant to 37 C.F.R. § 41.202. Applicants present herein a proposed Count and a complete showing of the information required by 37 C.F.R. § 41.202 with regard to the application as presently amended. The required information is set forth below under headings that correspond to the subsections of 37 C.F.R. § 41.202. In order to facilitate consideration by the Examiner, the Appendices attached hereto, which are summarized in the following table, further support the showings required under 37 C.F.R. § 41.202.

Accordingly, Applicants respectfully request that an interference be declared between the above-captioned application and the Short '449 patent.

Table of Appendices

Appendix A: Exemplary support in the present application for the pending claim of the present application.

Appendix B: A proposed Count.

Appendix C: A side-by-side comparison of Claims 1-12 of the Short '449 patent and the proposed Count.

Appendix D: A side-by-side comparison of Claim 275 of the present application, with the proposed Count.

Appendix E: A copy of the Short '449 patent

Appendix F: A copy of the present Patten '221 application.

Appendix G: A comparison of the relative filing dates for Short and Patten.

REQUEST FOR INTERFERENCE

I. IDENTIFICATION OF A PATENT THAT INCLUDES SUBJECT MATTER THAT INTERFERES WITH THIS APPLICATION

A patent that claims subject matter that interferes with subject matter claimed in the present Patten '221 application is: U.S. Patent No. 6,605,449 by Short ("the Short '449 patent") for "SYNTHETIC LIGATION REASSEMBLY IN DIRECTED EVOLUTION". The Short '449 patent issued from U.S. Application Serial No. 09/594,459, filed June 14, 2000 ("the Short '459 application"). On the face of the Short '449 patent, the 'Short '459 patent is indicated to be a continuation-in-part of Application Serial No. 09/332,835, filed on June 14, 1999 ("the Short '835 application"), now abandoned. Diversa Corporation, San Diego, California, is identified as assignee on the face of the Short '449 patent.

II. PRESENTATION OF A PROPOSED COUNT

The interfering subject matter between the Patten '221 application and the Short '449 patent relates to methods of producing libraries of chimerized enzymes. Attached Appendix B sets forth a proposed Count in chart form for the Examiner's consideration.

The proposed Count is an alternative Count, prepared after consideration of the subject matter claimed by the respective parties, which describes the interfering subject matter. The proposed Count comprises, in the alternative, Claim 6 of the Short '449 patent, or Claim 275 of the Patten '221 application. The alternative claims which comprise the count describe the same invention within the meaning of 37 C.F.R. § 41.203(a) as shown by

comparison of the claims in Appendix B, and further demonstrated by the analysis in Section III below.

III. THE PROPOSED COUNT INCLUDES DIFFERENT TERMS USED BY THE RESPECTIVE PARTIES TO DESCRIBE THE SAME INVENTION

The proposed Count is in alternative form in part because of the different language utilized by the respective parties to describe the interfering subject matter. A comparative analysis of the language used in the respective specifications is presented below.

A. "Progeny library" v. "library"

The Short '449 patent describes progeny molecules as those molecules "obtained by mutagenization of the parental set". (Col. 24, ll. 5-10) The Patten '221 application states that "starting DNA segments are recombined...to generate a diverse library of recombinant DNA segments. In general, the starting segments and the recombinant libraries generated include full-length coding sequences..." (p. 16, ll. 18-25) As such, the "progeny library" of Short and the "library" obtained by mutagenizing the starting DNA segments are the same.

B. "Predetermined polynucleotide sequence" v. "defined polynucleotide sequence"

The Short '449 patent states that "non-stochastic or non-random mutagenesis is exemplified by a situation in which a progenitor molecular template is mutated (modified or changed) to yield a progeny molecule having one or more **predetermined** mutations." (Col. 2, ll. 48-52; Emphasis added.) The Patten '221 application states that "'Coarse grain shuffling' generally involves the exchange or recombination of segments of nucleic acids, whether **defined** as functional domains, exons, restriction endonuclease fragments, or otherwise arbitrarily **defined** segments." (p. 12, l. 35 – p. 13, l. 2) As such, the

"predetermined sequences" of the Short '449 patent and the "defined sequences" of the Patten '221 application are the same, because they both relate to the knowledge of the desired mutation prior to making the mutation.

C. "Building block sequences" v. "polynucleotide segments"

The Short '449 patent states that the "building block sequences" may be single-stranded or double-stranded polynucleotides". (Col. 10, ll. 11-12) The Short '449 patent further states that "a unique overall assembly order can also be achieved... by stepping the assembly of the building blocks in a deliberately chosen sequence". (Col. 11, l. 67 – Col. 12, l. 5) Likewise, the Patten '221 application notes that "segments of nucleic acids" can be "defined as functional domains, exons, restriction endonuclease fragments, or otherwise arbitrarily defined segments." (p. 12, l. 35 – p. 13, l. 2) As such, the "building block sequences" of the Short '449 patent and the "defined sequences" of the Patten '221 application are the same, because they both relate to "arbitrarily" or "deliberately" chosen nucleic acid "chunks" which are the starting materials for making the desired end product.

D. "Non-random order" v. "ordered fashion"

The Short '449 patent states that the chimeric nucleic acid molecules are produced non-stochastically, (i.e., non-randomly) such that the "overall assembly order [that] is chosen by design" (e.g., Col. 10, ll. 32-33). Likewise, the Patten '221 application states that the gene segments are reassembled in an "ordered fashion" (p. 33, l. 12). As such, an order which is not random, is "ordered", and therefore the elements of Short Claim 6 and Patten Claim 275 are the same.

E. "Enzymes or fragments thereof" v. "full-length enzymes"

"Full-length enzymes", as recited in Claim 275 of the Patten '221 application are one member of the two-member Markush group of "enzymes or fragments thereof" recited in Claim 6 of the Short '449 patent. Applicants submit that the application of the claimed method to "fragments" of enzymes is not patentable, and as such, Applicants did not add that recitation to Claim 275. Because the "full-length" enzymes of Claim 275 of the Patten '221 application are coextensive with the "enzymes" of Claim 6 of the Short '449 patent, this element of the claims should be considered to be substantially the same, and thus, reflecting interfering subject matter between the Short '449 patent and the Patten '221 application.

F. "Sequences delineated by demarcation points selected from aligned progenitor sequences" v. "borders defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences"

The Short '449 patent discusses determining the ends of what will be "building block" sequences, by aligning a number of substrates and looking for homology therebetween:

> Thus according to one aspect of this invention, the sequences of a plurality of progenitor nucleic acid templates are aligned in order to select one or more demarcation points, which demarcation points can be located at an area of homology, and are comprised of one or more nucleotides, and which demarcation points are shared by at least two of the progenitor templates. The demarcation points can be used to delineate the boundaries of nucleic acid building blocks to be generated. Thus, the demarcation points identified and selected in the progenitor molecules serve as potential chimerization points in the assembly of the progeny molecules. (Col. 52, ll. 37-48)

Likewise, the Patten '221 application at p. 38, ll. 18-28, describes the same such process:

> In some embodiments of the invention, a search of a region of sequence space defined by a set of substrates, such as members of a gene family, having less than about 80%, more typically, less than about 50% homology, is desired. This region, which can be part or all of a gene or a gene is arbitrarily

> delineated into segments. The segment borders can be chosen randomly, based on correspondence with natural exons, based on structural considerations (loops, alpha helices, subdomains, whole domains, hydrophobic core, surface, dynamic simulations), and based on correlations with genetic mapping data.

As such, "sequences delineated by demarcation points selected from aligned progenitor sequences" and "borders defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences" are the same.

G. "Non-stochastically reassembling" v. "reassembling"

If reassembly is characterized as either "stochastic" or "non-stochastic", then "non-stochastic" is one of merely two members of a Markush group. "Non-stochastically" reassembling is not a patentable distinction, because, as Short admits, "Currently available technologies in directed evolution include methods for achieving stochastic (i.e., random) mutagenesis and methods for achieving non-stochastic (non-random) mutagenesis." The Patten '221 application discloses that the design for mutagenesis can be random or non-random (see, Section F, above). As such, "non-stochastically reassembling" is not patentably distinct from "reassembling".

H. "Overall assembly order is achieved" v. "reassembled in an ordered fashion"

Achieving an overall assembly order is the same as reassembling in an ordered fashion. See Section D, above.

IV. IDENTIFICATION OF CLAIMS OF THE SHORT '449 PATENT THAT CORRESPOND TO THE PROPOSED COUNT

Claim 6 of the Short '449 patent is identical to an alternative of the Proposed Count and should be designated to correspond to the Proposed Count. Further, Claims 1-12 of the Short '449 patent are obvious over the Proposed Count and should also be designated as

corresponding to the proposed Count. A comparison of each of these claims with the Proposed Count is presented in Appendix C.

V. THE CLAIMS OF THE PATTEN '221 APPLICATION THAT CORRESPOND TO THE PROPOSED COUNT

Claims 1-15 and 274 of the Patten '221 application have been canceled. Claim 275 corresponds to the proposed count, because it is identical to an alternative of the proposed Count. Claim 275 represents a substantial copy of Claim 6 of the Short '449 patent and would be obvious over the proposed Count. Appendix D provides a side-by-side comparison of pending Claim 275 of the Patten '221 application with the proposed Count.

VI. APPLICANTS WILL PREVAIL ON PRIORITY

The present Patten '221 application was filed on August 22, 2003, and is a continuation of U.S. Application Serial No. 09/559,671, filed April 27, 2000 ("the 'Patten '671 application"), now U.S. Patent No. 6,613,514 ("the Patten '514 patent"), which is a continuation of U.S. Application Serial No. 08/769,062, filed December 18, 1996 ("the Patten '062 application"), now U.S. Patent No. 6,335,160 ("the Patten '160 patent"). Even if Short were granted the benefit of its Short '835 application, filed on June 14, 1999 (from which the Short '459 patent claims to be a continuation-in-part), Patten would still be designated Senior Party in the interference, because its '062 application was filed approximately two and a half years prior to the Short '835 application. Therefore, Patten will clearly prevail on priority.

The specifications of the Patten '221, '671, and '062 applications are essentially identical. As such, exemplary support for Claim 275 in all three applications is provided in Appendix A.

VII. A CLAIM CHART SHOWING EXEMPLARY WRITTEN DESCRIPTION OF THE ADDED CLAIMS IS ATTACHED

Exemplary support for pending Claim 275 can be found throughout the specification and claims as originally filed, at least as shown in Appendix A, attached.

VIII. CHARTS SHOWING CONSTRUCTIVE REDUCTION TO PRACTICE WITHIN THE SCOPE OF THE PROPOSED COUNT ARE ATTACHED

Appendix A, attached, shows exemplary support for Claim 275 in the present application, which is a continuation of the 'Patten '671 application, which is a continuation of

the Patten '062 application. The specifications of the Patten '221, '671, and '062 applications are essentially identical. Thus, Appendix A, also serves to show constructive reduction to practice within the scope of the Count in the '221, '671 and '062 applications.

IX. CONCLUSION

Present Claim 275 is substantially copied from Claim 6 of the Short '449 patent, using the corresponding terminology of the Patten '221 application. Claim 275 was added on August 6, 2004, prior to one year after the issuance of the '449 patent on August 12, 2003. As such, Applicants' Claim 275 is not barred by 35 U.S.C. §135(b).

In view of the foregoing, Applicants respectfully request that an interference be declared employing the proposed Count set forth in attached Appendix B, with Claims 1-12 of the Short '449 patent, and Claim 275 of the present Patten '221 application being designated as corresponding to the proposed Count.

Furthermore, exemplary support in the '062 application for at least one embodiment within the scope of the proposed Count is shown in Appendix A. Since the Patten '221 application was filed December 18, 1996, well prior to the earliest Short '835 application, filed June 14, 1999, Patten should be designated as senior party. Such action is respectfully requested.

Should the Examiner feel that there are any issues outstanding after consideration of this paper, the Examiner is invited to contact Applicant's undersigned representatives to expedite prosecution. An interview regarding the present Request is requested at the Examiner's earliest convenience.

Respectfully submitted,

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APPENDIX A

EXEMPLARY SUPPORT[1] IN THE PATTEN '221, '671 AND '069 APPLICATIONS FOR CLAIM 275 AS CURRENTLY PENDING

Claim	Exemplary Support
275. A method of producing a library	p. 2, l. 24 – p. 3, l. 5, Claim 16 ("a method...to generate a library..."); p. 16, ll. 18-20 ("starting DNA segments are recombined...to generate a diverse library of recombinant DNA segments")
comprised of chimerized	p. 31, ll. 32-35 ("nucleic acids encoding protein modules can be exchanged...to generate novel and functional chimeric polyketides"); p. 37, ll. 20-21 ("A library of 10^4 chimeric interferon genes..."); p. 56, ll. 7-10 ("Similarly, chimeric polymerase libraries are made by breeding existing thermophilic polymerases..."); p. 74, ll. 17-18 ("one could make chimeras between IL2 and IL4, 7, 9, or 15 that also can bind the IL2 receptor alpha, beta and gamma chains..."); p. 80, ll. 3-6 ("construct libraries of chimeras between the mammalian G alpha protein(s)...")
but defined polynucleotide sequences	Claim 16 ("a first and second substrate molecules ...comprise defined segments")
each of which is comprised of a defined number of polynucleotide segments	Claim 16 ("a first and second substrate molecules ...comprise defined segments"); p. 32, l. 6 – p. 34, l. 9 (e.g., "assemble multiple segments"); Example III, p. 89, l. 36 – p. 93, l. 9 (e.g., "The modeled structure...has been divided into nine segments based on a combination of criteria of maintaining secondary structure elements as single units and placing/choosing placement of the segment boundaries in regions of high identity.")
that are assembled in an ordered fashion,	p. 33, l. 12 ("are reassembled in an ordered fashion...")
the method comprising:	p. 2, l. 29 ("the method comprising...")
a) generating a plurality of defined polynucleotide segments of substrate nucleic acid sequences	p. 29, ll. 22-27 ("The coarse grain methods allow one to exchange chunks of genetic material between substrate nucleic acids thereby limiting diversity in the

[1]The identified support is merely exemplary, and is not meant to be exhaustive. Applicant reserves the right to cite additional support at a later time, if necessary.

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	resulting recombinants to exchanges or substitutions of domains, restriction fragments, oligo-encoded blocks of mutations, or other arbitrarily defined segments..."); p. 32, ll. 9-11 ("multiple segments that have been separately evolved..."); p. 32, ll. 17-20 ("Boundaries defining segments of a nucleic acid sequence of interest...")
that encode full-length enzymes,	p. 43, ll. 18-20 ("this technique can be used to evolve bovine intestinal alkaline phosphatase (BIAP)..."; p. 82, ll. 16-25 ("Evolution of BIAP...the oligonucleotides are assembled into full-length genes as described above."); p. 16, ll. 22-24 ("In general, the starting segments and the recombinant libraries generated include full-length coding sequences...")
and wherein the borders defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences; and	p. 32, ll. 17-20 ("Boundaries defining segments of a nucleic acid sequence of interest preferably lie in intergenic regions, introns, or areas of a gene not likely to have mutations of interest; p. 38, ll. 23-28 ("This region, which can be part or all of a gene or a gene is arbitrarily delineated into segments. The segment borders can be chosen randomly, based on correspondence with natural exons, based on structural considerations (loops, alpha helices, subdomains, whole domains, hydrophobic core, surface, dynamic simulations), and based on correlations with genetic mapping data.)
b) reassembling said defined polynucleotide segments in order	p. 33, l. 12 ("reassembled in an ordered fashion")
thereby producing the library of chimerized but defined polynucleotide sequences,	p. 31, ll. 32-35 ("nucleic acids encoding protein modules can be exchanged...to generate novel and functional chimeric polyketides"); p. 37, ll. 20-21 ("A library of 10^4 chimeric interferon genes..."); Claim 16 ("a first and second substrate molecules ...comprise defined segments"); p. 56, ll. 7-10 ("Similarly, chimeric polymerase libraries are made by breeding existing thermophilic polymerases..."); p. 74, ll. 17-18 ("one could make chimeras between IL2 and IL4, 7, 9, or 15 that also can bind the IL2 receptor alpha, beta and gamma chains..."); p. 80, ll. 3-6 ("construct libraries of chimeras between the mammalian G alpha protein(s)...")
such that said segments are reassembled	p. 33, l. 12 ("reassembled in an ordered fashion")

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in an ordered fashion	
for each chimerized but defined polynucleotide sequences encoding full-length enzymes.	p. 31, ll. 32-35 ("nucleic acids encoding protein modules can be exchanged...to generate novel and functional chimeric polyketides"); p. 37, ll. 20-21 ("A library of 10^4 chimeric interferon genes..."); Claim 16 ("a first and second substrate molecules ...comprise defined segments"); p. 56, ll. 7-10 ("Similarly, chimeric polymerase libraries are made by breeding existing thermophilic polymerases..."); p. 74, ll. 17-18 ("one could make chimeras between IL2 and IL4, 7, 9, or 15 that also can bind the IL2 receptor alpha, beta and gamma chains..."); p. 80, ll. 3-6 ("construct libraries of chimeras between the mammalian G alpha protein(s)...")

APPENDIX B

THE PROPOSED COUNT

Claim 6 of the Short '449 patent (incorporating the limitations of Claim 1, from which it depends)	**OR**	**Claim 275 of the Patten '221 application**
A method of producing a progeny library comprised of chimerized but pre-determined polynucleotide sequences each of which is comprised of a pre-determined number of building block sequences that are assembled in non-random order, the method comprising: generating a plurality of pre-determined nucleic acid building block sequences obtained from polynucleotide sequences that encode enzymes or fragments thereof and comprised of sequences delineated by demarcation points selected from aligned progenitor sequences; and non-stochastically reassembling said nucleic acid building block sequences to produce said chimerized but pre-determined polynucleotide sequences, such that a designed overall assembly order is achieved for each of said chimerized but pre-determined polynucleotide sequence.		A method of producing a library comprised of chimerized but defined polynucleotide sequences each of which is comprised of a defined number of polynucleotide segments that are assembled in an ordered fashion, the method comprising: a) generating a plurality of defined polynucleotide segments of substrate nucleic acid sequences that encode full-length enzymes, and wherein the borders defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences; and b) reassembling said defined polynucleotide segments in order thereby producing the library of chimerized but defined polynucleotide sequences, such that said segments are reassembled in an ordered fashion for each chimerized but defined polynucleotide sequences encoding full-length enzymes.

APPENDIX C

CLAIMS OF THE SHORT '449 PATENT THAT CORRESPOND WITH THE PROPOSED COUNT COMPARED WITH THE PROPOSED COUNT

Short '449 Patent Claim	Comparison with the proposed Count
1. A method of producing a progeny library comprised of chimerized but pre-determined polynucleotide sequences each of which is comprised of a pre-determined number of building block sequences that are assembled in non-random order, the method comprising: (a) generating a plurality of pre-determined nucleic acid building block sequences comprised of sequences delineated by demarcation points selected from aligned progenitor nucleic acid sequences; and (b) non-stochastically assembling said nucleic acid building block sequences to produce said chimerized but pre-determined polynucleotide sequences, such that a designed overall assembly order is achieved for each of said chimerized but pre-determined polynucleotide sequence.	Claim 6, which is dependent from, and incorporates all the limitations of Claim 1, is one alternative of the Count. As such, Claim 1 is anticipated by the Count, and should correspond thereto.

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Short '449 Patent Claim	Comparison with the proposed Count
2. The method of claim 1 where the progenitor nucleic acid sequences comprise sequences derived from an uncultivated organism or an environmental sample.	Claim 6, which is dependent from, and incorporates the limitations of Claim 2, is one alternative of the Count. As such, Claim 2 is anticipated by the Count, and should correspond thereto. Moreover, deriving sequences from an uncultivated organism or an environmental sample would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* Brennan (1996) *Chemical and Eng. News* 74:31-33
3. The method of claim 1 where the progenitor nucleic acid sequences are comprised of genomic nucleic acid sequences.	Claim 6, which is dependent from, and incorporates the limitations of Claim 3, is one alternative of the Count. As such, Claim 3 is anticipated by the Count, and should correspond thereto. Moreover, starting with genomic sequences is a mere design choice, which would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230[1] at p. 36, ll. 29-31 {"The starting exon DNA may be synthesized de novo from sequence information, or may be present in any nucleic acid preparation (e.g., genomic, cDNA, libraries, and so on)."}

1 Note that WO 98/27230 is the 1998 publication of the PCT application corresponding to the present Patten '221 application specification.

APPENDIX C

Short '449 Patent Claim	Comparison with the proposed Count
4. The method of claim 1, where the progeny library is comprised of at least 10^{10} different pre-determined progeny molecular sequences.	Claim 6, which is dependent from, and incorporates the limitations of Claim 4, is one alternative of the Count. As such, Claim 4 is anticipated by the Count, and should correspond thereto. Moreover, progeny library is comprised of at least 10^{10} different pre-determined progeny molecular sequences would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230 at p. 16, ll. 18-22 and p. 91, ll. 26-28{"The starting DNA segments are recombined by any of the recursive sequence recombination formats provided herein to generate a diverse library of recombinant DNA segments. Such a library can vary widely in size from having fewer than 10 to more than 10^5, 10^9, or 10^{12} members." "Thus, the potential diversity encoded by permutation of all of this naturally occurring diversity is: $2^{57} \times 3^{15} \times 4^4 = 5.3 \times 10^{26}$"}

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Short '449 Patent Claim	Comparison with the proposed Count
5. The method of claim 1, where the progeny library is comprised of at least 10^{15} different pre-determined progeny molecular sequences.	Claim 6, which is dependent from, and incorporates the limitations of Claim 5, is one alternative of the Count. As such, Claim 5 is anticipated by the Count, and should correspond thereto. Moreover, progeny library is comprised of at least 10^{10} different pre-determined progeny molecular sequences would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230 at p. 16, ll. 18-22 and p. 91, ll. 26-28{"The starting DNA segments are recombined by any of the recursive sequence recombination formats provided herein to generate a diverse library of recombinant DNA segments. Such a library can vary widely in size from having fewer than 10 to more than 10^5, 10^9, or 10^{12} members." "Thus, the potential diversity encoded by permutation of all of this naturally occurring diversity is: $2^{57} \times 3^{15} \times 4^4 = 5.3 \times 10^{26}$"}
6. The method of any of claims 1-5, where the nucleic acid building block sequences are obtained from polynucleotide sequences that encode enzymes or fragments thereof.	Claim 6 is one alternative of the Count.

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Short '449 Patent Claim	Comparison with the proposed Count
7. The method of any of claims 1-5, where the nucleic acid building block sequences are assembled to produce polynucleotide encoding biochemical pathways from one or more operons or gene clusters of portions thereof.	Claim 7 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, assembling building block sequences to produce polynucleotide encoding biochemical pathways from one or more operons or gene clusters of portions thereof would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230 at p. 13, ll. 9-13 {"For example, coarse grain searches are often better suited for optimizing multigene clusters such as polyketide operons, whereas fine grain searches are often optimal for optimizing a property such as protein expression using codon usage libraries."}
8. The method of any of claims 1-5, where the nucleic acid building block sequences are obtained from polynucleotide encoding polyketides2 or fragments thereof.	Claim 8 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, assembling building block sequences obtained from polynucleotides (or fragments thereof) which encode enzymes which produce polyketides[2] would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230 at p. 13, ll. 9-13 {"For example, coarse grain searches are often better suited for optimizing multigene clusters such as polyketide operons, whereas fine grain searches are often optimal for optimizing a property such as protein expression using codon usage libraries."}

2 Note that Short '449 Claim 8 is not technically correct, and therefore indefinite, because polynucleotides do not encode polyketides; rather, polynucleotides encode enzymes which produce polyketides.

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Short '449 Patent Claim	Comparison with the proposed Count
9. The method of any of claims 1-5, where the nucleic acid building block sequences are obtained from polynucleotide encoding antibodies or antibody fragments or other peptides or polypeptides.	Claim 9 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, obtaining building block sequences from an antibody would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230, p. 40, ll. 35-37 {"For example, this format is preferred for the in vivo affinity maturation of an antibody by RSR."}
10. The method of any of claims 1-5, where the step of (b) non-stochastically assembling said nucleic acid building blocks is performed to generate a display library comprised of polypeptides or antibodies or peptidomimetic antibodies or antibody variable region sequences suitable for affinity interaction screening.	Claim 10 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, generating a display library comprised of antibody regions would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230, p. 66, ll. 1-2 {"For example, the affinity of an antibody for a ligand can be improved using mammalian surface display and RSR."}
11. The method of any of claims 1-5, further comprising the step of (c) screening said progeny library to identify an evolved molecular property.	Claim 11 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, screening for an evolved molecular property would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230, p. 8, ll. 31-33 {"A further aspect of the invention is a method for screening a library of protease mutants to obtain an improved protease..."}

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Short '449 Patent Claim	Comparison with the proposed Count
12. The method of claim 1, where step of (c) is comprised of expression screening to identify an evolved molecular property.	Claim 12 incorporates the limitations of Claim 1, which is obvious in view of the Count. Moreover, expression screening to identify an evolved molecular property would have been obvious to one of ordinary skill in the art at the time the application for the '449 patent was filed. *See, e.g.,* WO 98/27230, p. 9, ll. 32-34 {"A further aspect of the invention is a method for screening a library of mutants of a DNA substrate encoding a protein for an evolved DNA substrate, comprising: (a) providing a library of mutants, the library comprising an expression vector; (b) transfecting a mammalian host cell with the library of (a), wherein mutant protein is expressed on the surface of the cell; (c) screening or selecting the products of (b) with a ligand for the protein..."}

APPENDIX D

PENDING CLAIM 275 OF THE PATTEN '221 APPLICATION THAT CORRESPONDS WITH THE PROPOSED COUNT COMPARED WITH THE PROPOSED COUNT

Patten '221 Application Claim	Comparison with the proposed Count
275. A method of producing a library comprised of chimerized but defined polynucleotide sequences each of which is comprised of a defined number of polynucleotide segments that are assembled in an ordered fashion, the method comprising: a) generating a plurality of defined polynucleotide segments of substrate nucleic acid sequences that encode full-length enzymes, and wherein the borders defining the polynucleotide segments are selected from the aligned substrate nucleic acid sequences; and b) reassembling said defined polynucleotide segments in order thereby producing the library of chimerized but defined polynucleotide sequences, such that said segments are reassembled in an ordered fashion for each chimerized but defined polynucleotide sequences encoding full-length enzymes.	Claim 275 is one alternative of the Count

APPENDIX E

U.S. Patent No. 6,605,449 to Short

APPENDIX F

U.S. Application No. 10/646,221 as published under Publication No. 20040248253